OVERVIEW

• Clinic ready - clinical development candidate declared, a potent, orally bioavailable dual FLT3 / Aurora kinase inhibitor

• Single agent dose dependent growth inhibition in FLT3 ITD positive human AML xenograft model in vivo

• Mutation-driven resistance to selective FLT3 inhibition overcome in AML in vivo model

• Capacity and expertise to run first-in-man and paediatric clinical trials with PK/PD support

THE OPPORTUNITY

Cancer Research UK is seeking a co-development or licensing partner to take this Clinical Development Candidate into Phase I clinical studies.

The project is ready to progress to the clinic, with pre-clinical toxicology studies completed, bulk API manufactured and a clinical protocol prepared. The initial indication is acute myeloid leukemia (AML), where there is an unmet need for novel therapeutics. Dual FLT3/Aurora kinase inhibitors also have the potential for the treatment of other cancers, including neuroblastoma and pancreatic, neuroendocrine, prostate cancer targeting Aurora A-MYCN.

BACKGROUND AND THERAPEUTIC RATIONALE

Mutations of the FLT3 gene represent one of the most common mutations in AML. Internal tandem duplication (FLT3-ITD) mutations or point mutations of the tyrosine kinase domain (FLT3-TKD) both result in constitutive FLT3 kinase activation. FLT3-ITD occurs in 20-35% of adults and 15% of children with AML (AML FLT3-ITD) and confers a poor prognosis in both age groups. FLT3-TKD mutations occur in approximately 7% of all age groups. The clinical impact of FLT3 inhibitors has thus far been limited by transient responses when used as single agents and the emergence of acquired resistance following treatment.

Aurora kinases A and B play a key role in mitosis. Aurora kinase inhibitors are emerging as promising agents in the treatment of AML, and single agent Phase I-II clinical trials of an Aurora B inhibitor and an Aurora A inhibitor in patients with advanced AML have shown response rates of 25% and 17% respectively [1,2].

The clinical development candidate targets these two validated targets in AML – FLT3 (including clinically relevant FLT3-ITD-TKD mutant forms) and Aurora kinases. The strategy of dual FLT3 / Aurora inhibition in a single agent has the potential to overcome the need for combination therapies in AML, and is predicted to have improved efficacy in FLT-ITD+ AML and reduced susceptibility to resistance mediated by both secondary FLT3-TKD mutations [3] and high levels of FLT3 ligand.

POTENT AND SELECTIVE DUAL FLT3/AURORA INHIBITORS WITH IN VIVO EFFICACY

Novel compounds with low nM activity against both FLT3 (including FLT3-ITD+) and Aurora (A and B) kinases have been identified. Mechanism of action and in vivo studies featuring the lead series have been published [4-7]. Compounds from the lead series are ATP-competitive, have good in vitro ADME properties and have shown anti-proliferative activity in a range of human tumour cell lines including human
FLT3-ITD-positive AML cell lines [5] and to be efficacious in both leukemic and solid tumours models - human colon carcinoma HCT116 and transgenic and primary transplant MYCN-driven neuroblastomas. Compounds from the lead series also induce a reduction in tumour [18F]FLT retention detectable by non-invasive PET imaging [8].

The Clinical Development Candidate:

- inhibits the growth of MV4-11 (Figure 1) and MOLM-13 human FLT3-ITD AML xenografts in vivo
- inhibits FLT3-ITD within clinically relevant TKD mutant forms
- overcomes resistance to selective FLT3 inhibition in vivo (MOLM-13- MLN518-resistant (doubly mutated FLT3-ITD + FLT3-D835Y) human tumour xenografts – which are also resistant to AC220 and the more promiscuous kinase inhibitor Sorafenib; Figure 2)
- exhibits in vitro and in vivo modulation of signalling downstream of FLT3 and Aurora kinases consistent with a mechanism of action via dual inhibition in leukemic models
- is less susceptible to the effects of FLT3 ligand compared with the selective FLT3 inhibitors AC220 and MLN518 in vitro

### SUMMARY OF CLINICAL DEVELOPMENT CANDIDATE DATA

| Biochemical Kd (nM) | Aurora A = 7.5; Aurora B = 48
|FLT3 = 6.2; FLT3-ITD = 38; FLT3 (D835H) = 11; FLT3 (D835Y) = 14; FLT3 (K663Q) = 5.1; FLT3 (R834Q) = 110; FLT3 (N841I) = 16 |
|Biochemical selectivity | KINOMEScan (442 kinase panel at a concentration of 1 μM), S(10) selectivity score = 0.057 |
|Cellular efficacy: 3d MTS, Gi50 (μM) | FLT3-ITD AML cell lines: MOLM-13 = 0.104; MV4-11 = 0.291; MLN518 FLT3 inhibitor resistant AML cell line MOLM-13-RES = 0.18 |
|Cellular biomarker activity IC50 (μM) | Inhibition of Aurora-A T288 phosphorylation = 0.038; Inhibition of Aurora-B H3 phosphorylation = 0.148; Inhibition of STAT5 and FLT3 phosphorylation = 0.005-0.006 |
|In vivo pharmacokinetic profile | Mouse: T1/2 = 0.64 (h); Cl = 0.058 L/h; Cmax: = 1.83 μM; AUClast (iv; nmol h) = 3.7 μM·h; F oral = 100%
| R at: T1/2 = 2.6 (h); Cl = 0.057 L/h; Cmax: = 2.53 μM; AUClast (iv; nmol h) = 32.6 μM·h; F oral = 82%
|Estimated human plasma clearance = 6 ml/min/kg based on allometric scaling, 2ml/min/kg based on Physiological Base PK |

### INTELLECTUAL PROPERTY


### ORIGINATING INSTITUTE

This programme, led by Dr Spiros Linardopoulos, originates from the Cancer Research UK Cancer Therapeutics Unit headed by Professor Rajesh Chopra and the Breast Cancer Now Research Centre at The Institute of Cancer Research. The Institute of Cancer Research, in partnership with The Royal Marsden, is at the forefront of cancer research and has a unique drug discovery and development facility on site. Capacity and expertise to run first-in-man and paediatric clinical trials with PK/PD support would be available through The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research. Many drugs discovered or developed at The Institute of Cancer Research have successfully entered the clinic and several have entered the market.

### REFERENCES

1. Lowenberg B., et al., 2011 PMID: 21976672
4. Bevetsias V et al., 2012. PMID: 23043539
5. Bavetsias V., et al., 2010. PMID:20565112
8. Chan F., et al., 2007 PMID:18089709

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